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Incretin Hormones and their effects in Type 2 Diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized as having pancreatic β-cell dysfunction, insulin resistance and hyperglycemia (Stephens, 2010, p. 491). T2DM affected 29.1 million Americans or 9.3% of the population in 2012 and was the seventh leading cause of death in the United States in 2010 ("ADA Statistics," 2014), with many of these patients finding it difficult to achieve or maintain adequate glycemic control despite making lifestyle changes and pharmacologic interventions (Freeman, 2007).

Disease management of T2DM requires a comprehensive plan including medication therapy, education and active involvement of the patient, with the goal of therapy to lower the A1C (Robertson, 2012). Incretin mimetics are a class of medications available for treating patients with T2DM; they mimic the action of incretin hormones released during nutrient absorption (Freeman, 2007). Patients with T2DM have an impaired incretin response (Pratley, n.d., p. 8).

Incretin Effect

The incretin effect is the secretion of insulin after ingestion of food compared to the isoglycemic intravenous glucose challenges (Ahren, 2013). Incretins are peptide hormones that originate in the gut and increase the effectiveness of insulin secretion after meal ingestion in a glucose-dependent manner (Campbell & Drucker, 2013). Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1) are the two dominant incretin hormones and are responsible for the so-called "incretin effect" (Campbell & Drucker, 2013, p. 819). GLP-1 and GIP play an essential role in maintaining normal glucose-homeostasis and in particular postprandial glucose levels ("Incretin physiology," 2014). Incretin therapy is associated with a low risk of adverse events such as hypoglycemia (Ahren, 2013).

GIP

GIP is a 42 amino acid peptide (Drucker, 2006, p. 153) secreted from duodenum K-cells in the proximal small intestine and is transported through the blood (Pratley, n.d., p. 7). Nutrient intake stimulates GIP production; GIP levels are low in the fasted state and will rise within minutes of food consumption (Drucker, 2006). GIP has direct effects on insulin secretion that are mediated through a specific receptor for GIP on β cells (Pratley, n.d., p. 8). GIP has a short half-life of seven minutes (Cornell, 2013), and is eliminated from the circulation via the kidneys (Drucker, 2006). GIP is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4), an exopeptidase (Drucker, 2013). According to Drucker (2006), GIP does not appear to be important for control of fasting glucose.

GLP-1

GLP-1 is produced in enteroendocrine cells in the distal small bowel and colon from L-cells (Drucker, 2006, p. 153) and binds to a G-protein coupled receptor in the endocrine pancreas (Burgmaier, Heinrich, & Marx, 2012). Via stimulation of adenylyl cyclase and cyclic adenosine monophosphate (cAMP) production (Burgmaier et al., 2012, p. 290), GLP-1 increases insulin secretion from pancreatic β cells and inhibits glucagon secretion from α cells, increases insulin synthesis, confers glucose sensitivity to glucose-resistant β cells, stimulates β cell proliferation and regeneration, and inhibits β cell apoptosis (Campbell & Drucker, 2013). GLP-1 plasma levels rise within minutes after food intake and has a short half-life of two minutes and like GIP is degraded rapidly by DPP-4 and excreted via the kidneys (Drucker, 2013). GLP-1 lowers blood sugar levels and body weight by inhibiting appetite by enhancing satiety through its hypothalamic action and by slowing gastric emptying, which results in a decreased influx of glucose into the circulation (Pratley, n.d., p. 8).

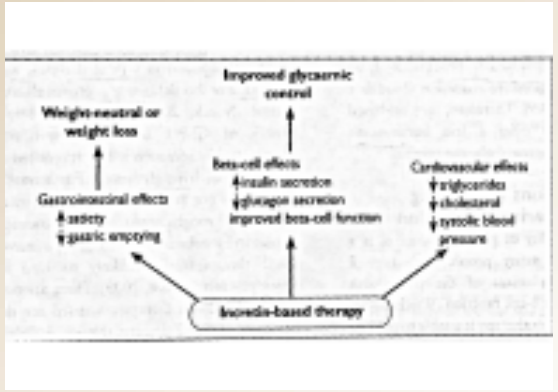
DPP-4

According to Drucker (2006, p. 154), both GLP-1 and GIP stimulate glucose-dependent insulin secretion via activation of their specific G protein-coupled receptors expressed directly on islet β cells. Both hormones stimulate insulin gene transcription, increase pancreatic β cell mass and protect against β cell apoptosis (Vilsboll & Knop, 2014, p. 2).

Incretin-based therapies are used as add-on therapy to conventional T2DM treatment improving glycemic control and is generally well tolerated (Capaldi, 2012). Two classes of incretin-based therapies are DPP-4 inhibitors and GLP-1 receptor agonists.

DPP-4 is the key enzyme responsible for inactivating GIP and GLP-1 and exists in two principal forms: a membrane anchored, largely extracellular protein capable of stimulation of intracellular signal transduction pathways independent of its enzymatic activity, and a circulating soluble enzyme which retains enzymatic activity (Drucker, 2006, p. 160). According to Drucker (2006), genetic evidence supports an essential role of DPP-4 in the control of glucose homeostasis.

DPP-4 inhibitors block the action of the enzyme that degrades GLP-1 by slowing the rapid degradation of GLP-1 to the metabolite GLP-1 (9-36) amide (Burgmaier et al., 2012, p. 290). DPP-4 inhibitors also decrease the degradation of other peptides that are substrates to DPP-4, including GIP and a variety of chemokines (Burgmaier et al., 2012, p. 290). According to Capaldi (2012), GLP-1 receptor agonists and DPP-4 inhibitors reduce glucose levels with low risk of hypoglycemia and GLP-1 receptor agonists are associated with weight loss, whereas DPP-4 inhibitors are weight neutral (Capaldi, 2012). DPP-4 inhibitors are rapidly absorbed and excreted by the kidneys; therefore renal function should be assessed before their use (Aye & Jennings, 2009, p. 197).



Implication for Nursing Care

GLP-1 receptor agonists are long-acting which make them resistant to GLP-1 inactivation by DPP-4 (Stephens, 2010). According to Capaldi (2012), self-monitoring of blood glucose is not needed to adjust the dose of the agent prescribed since GLP-1 action is glucose-dependent.

GLP-1 receptor agonists should be avoided in patients with gastroparesis, and patients need educated that nausea is most often transient, and they should be counseled to eat smaller meals (Williams & Prasad-Reddy, 2012, p. 371). Hypersensitivity reactions exist for DPP-4 inhibitors: anaphylaxis, angioedema, exfoliative skin conditions, and bronchial hyperreactivity. Angioedema was the most commonly reported hypersensitivity reactions of the DPP-4 inhibitors (Williams & Prasad-Reddy, 2012, p. 371). DPP-4 inhibitor-induced angioedema is related to reduced DPP-4 enzymatic activity and inhibited degradation of proinflammatory bradykinins and substance P (Williams & Prasad-Reddy, 2012, p. 371). Pancreatitis is listed as a precaution for GLP-1 agonists and DPP-4 inhibitors (Williams & Prasad-Reddy, 2012). GLP-1 agonists may prove to have a cardioprotective function that is both receptor-dependent and receptor-independent. Binding of the GLP-1 receptor in the myocardium stimulates an increase of inotropic action (Williams & Prasad-Reddy, 2012, p. 372).

The nurse practitioner (NP), often serving as the primary care provider has many options in treating the patient with T2DM. Treatment related side effects such as weight gain and hypoglycemia are usually a concern to the patient, which could deter the patient from following the treatment regimen prescribed (Bartol, 2012). Selecting treatments that minimize side effects can help patients feel more optimistic and motivate them to continue taking their medications (Bartol, 2012). Prior to starting an incretin-based drug therapy the NP should obtain an A1C and according to Bartol (2012), one month after initiation of incretin therapy to see if the incretin analog is lowering glucose levels. At the one month follow-up visit if the A1C is not improving, consider a change in the treatment regimen, and assess for nausea and weight loss at this follow-up visit (Bartol, 2012).

The incretin therapies are an established component of diabetes management and the NP can be a key player in educating and prescribing medications; NPs play an essential role in motivating their patients to become active participants in their diabetes management. Motivating and encouraging lifestyle changes will help the patient to achieve improved diabetes control (Bartol, 2012).

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